## REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-77 were presented for examination. Claims 1-40, 47-49, 52-65, and 74-77 were previously cancelled.

Claims 78-81 have been added to the application. These claims are similar to cancelled claims 62-65.

Claims 82-85 have also been added to the application. These claims are similar to cancelled claims 74-85.

Method claims 86-89 have been added to the application. These claims are similar to previously withdrawn claims 52-95. Applicant submits that these method claims are subject to rejoinder when the product claims from which they depend have been found to be allowable.

Claims 90-92, which relate to recombinant particles containing the vectors of the invention, have been added to the application. These claims are derived from claim 46 and cancelled claims 62 and 74.

Finally, claim 93 has been added to the application. This claim is derived from claims 41, 66, and 90.

Claims 41 and 66 have been amended to recite a polynucleotide "for transduction of cells." This amendment is supported, *inter alia*, at paragraphs [0164]-[0169] and paragraphs [0186]-[0187] of the published application. The recitation that the cPPT and CTS sequences are "cis-acting in reverse transcription" is supported, for example, at paragraph [0015]. Entry of these amendments is respectfully requested.

Applicant's invention relates to lentiviruses, such as HIV. The mechanism for reverse transcription of the HIV virus differs from that of oncogene retroviruses in that the plus strand (+strand) is synthesised in two distinct halves (*see* FIG. 1 in the published application). A downstream segment is initiated at a central copy of the polypurine tract (cPPT), characteristic of lentivirus genomes. Synthesis of the upstream plus strand is terminated after a discrete displacement of the strand at the center of the genome. Blocking the displacement of the strand by reverse transcriptase is governed by a new cis-acting sequence of the HIV genome: The CTS (central termination sequence). The final product of reverse transcription of lentiviruses is a linear DNA carrying a central structure spanning the strand over about a hundred nucleotides. *See* ¶ [0172] of published application.

The triple-stranded conformation of this central region is termed a DNA "triplex" sequence. Id. at [0017]-[0019]. This triplex DNA structure present at the center of linear DNA molecules generated during lentiviral reverse transcription, in particular in the HIV retrovirus, has been described by the inventors in different publications (Charneau *et al.*, J. Mol. Biol. 1994, 241, 651-662; Charneau *et al.*, Journal of Virology, May 1991, p 2415-2421; and Charneau *et al.*, Journal of Virology, 1992, vol. 66, p 2814-2820).

The inventors searched the determinants involved in the entry of the retrovirus genome into infected cell nuclei, which is known as the nuclear import mechanism. (Id. at p. 1, ll. 23-24.) In particular, the inventors worked from HIV, a member of the lentivirus family, and identified and isolated a viral determinant responsible for the

nuclear import of proviral DNA of HIV into target cells. They discovered that nuclear import was dependent on the DNA triplex. (Id. at p. 2, ll. 3-6.)

The implication of a DNA structure (DNA Flap) in a nuclear import mechanism had never been provided. There were no previous viral or cellular examples. Consequently, this mechanism of nuclear import and the role of the sequence DNA triplex was completely unpredictable. By no means were this discovery and the claimed vectors obvious at the date of the filing.

In addition, the inventors discovered that the DNA triplex is able to function in vectors, out of the natural context of the lentiviral genome, as a nuclear import determinant enabling the vector genome to enter the nucleus of target cells. (Specification at p. 2, ll. 6-8.). Starting from the identification of the central triplex DNA as the essential nucleotide sequence for entry of the retrovirus into the nucleus of a target cell, the inventors produced a novel lentiviral vector, including the nucleotides that form the triplex DNA region. The introduction of the nucleotides that form this DNA fragment into a vector system increases transduction of viral vectors into the cells by stimulating the amount of nuclear import of the vector DNA. (Id. at p. 3, ll. 21-25.)

Thus, Applicant's claims are directed to a recombinant, non-replicative, non-infectious, lentiviral transfer vector containing the nucleotides that form the central triplex DNA. The claims require a lentiviral DNA triplex that is out of its natural context in the lentiviral genome because "the vector is deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins." (Specification at p. 2, ll. 6-8, and p. 8, ll. 1-4.)

**Claims Rejections - 35 USC § 103**

Claims 41-46, 50, and 51 were rejected under 35 U.S.C. § 103(a) as being obvious over Verma *et al.* (WO 97/12622) in view of Charneau *et al.* (1994, hereinafter Charneau '94) and Charneau *et al.* (1992, hereinafter Charneau '92). According to the Office, claims 41-46, 50, and 51 are directed to a recombinant, non-replicative, non-infectious, lentiviral transfer vector deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins, comprising: (1) a polynucleotide comprising a cis-acting central polypurine tract ("cPPT"), and a cis-acting central terminator sequence ("CTS"), wherein the cPPT and CTS are of retroviral-like origin and derived from a retrotransposon and which form a triple-stranded sequence (DNA triplex); (2) a defined nucleotide sequence (transgene or sequence of interest); and (3) regulatory signals for reverse transcription, expression, and packaging, wherein the regulatory signals are of retroviral or retroviral-like origin; and wherein the DNA triplex transfers the defined nucleotide sequence into the nucleus of a cell. *Id.* at 3-4.

Claims 62-77 recited the additional limitation of a non-infectious particle, wherein the HIV Gag, Pol, and Env proteins are provided by one or more additional vector(s).

The Office contends that Verma discloses a recombinant, non-replicative, non-infectious retroviral transfer vector comprising: (1) a transgene encoding luciferase or β-galactosidase, and (2) retroviral regulatory signals, HIV-1 LTR and RRE. The Office further contends Verma discloses two additional vectors, a packaging construct comprising HIV Gag, Pol, Vif, Tat, Rev and Nef, and pseudotyping MLV vector comprising HIV Env. The Verma retroviral transfer vector does not comprise cPPT and CTS. Id. at 4.

According to the Office, Charneau '94 discloses that cPPT is an important cis-acting sequence for initiating DNA transcription by priming DNA synthesis. The Office contends that Charneau '94 further discloses a cis-acting HIV-1 CTS that is essential for terminating DNA synthesis by displacing the completed DNA strand, and Charneau '94 specifically discloses the nucleotide sequence of HIV-1 CTS. Charneau '94 does not disclose the nucleotide sequence of cPPT. *Id.*

Charneau '92 was cited because it discloses the nucleotide sequence of HIV-1 cPPT. According to the Office, Charneau '92 also discloses that cPPT is an important sequence for initiating DNA transcription. *Id.*

The Office concluded that it would have been obvious "to modify the Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, as taught by Charneau '92 and Charneau '94, upstream and downstream [of] the coding sequence of the transgene in the retroviral transfer vector taught by Verma *et al.*" *Id.*

Applicant respectfully transverses this ground for rejection and requests reconsideration for the following reasons.

It should be evident from Applicant's claims that Applicant's vector, and the other embodiments of the invention incorporating the vector, contain, among other things, two distinct elements:

(1) a polynucleotide for formation of a DNA triplex, and

(2) a defined nucleotide sequence, *e.g.*, a transgene or sequence of interest.

Applicant's claims also define the relationship between these two distinct elements: "[T]he DNA triplex transfers the defined nucleotide sequence into the nucleus of a cell." *See* claims 41, 66, and 93.

In addition, and not to be overlooked, is Applicant's discovery that the transduction efficiency of triplex-negative vectors is significantly reduced. A DNA triplex is essential in Applicant's invention. The vectors exhibit defective replication and transduction properties without it. *See* ¶¶ [0179]-[0190] of published specification.

Nevertheless, the Office contends that:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, as taught by Charneau'94, upstream and downstream [of] the coding sequence of the transgene in the retroviral transfer vector taught by Verma *et al.*

Office Action at 4-5.

There are two interpretations of this statement. First, the Office believes that it would have been obvious to use only the cPPT and CTS sequences with the transgene, eliminating all the other sequences of the triplex. An alternative interpretation of this statement is that the Office believes that it would have been obvious to insert the transgene into the sequence that forms the triplex, retaining all of the nucleotides that form the triplex.

If these modifications were made to Verma's vector, they would not produce Applicant's vector, which requires the nucleotides that form a triplex sequence, not simply the cPPT and CTS regions or the disrupted sequence that would result if the transgene was inserted between the cPPT and CTS sequences. *See* claims 41 and 66. Apparently overlooked by the Office is the fact that viruses in which the DNA is deprived

of the central triplex are defective for viral replication. *Id.* at [0172]. Thus, for this reason alone, a *prima facie* case of obviousness has not been made out, and the § 103 rejection should be withdrawn.

The § 103 rejection should be withdrawn for the additional reason that the Office has failed to make any findings of fact that the triplex sequence referenced in Applicant's claims will be formed if "the initiation signal, cPPT, and the termination signal, CTS, ... [are inserted] upstream and downstream [of] the coding sequence of the transgene in the retroviral transfer vector taught by Verma *et al.* as asserted in the Office Action." *See* Office Action at 4-5. The § 103 rejection is not sustainable without such findings.

The § 103 rejection should be withdrawn for the further reason that the Office has failed to make any findings of fact that the vector would have the replication and cell transduction properties recited in the claims if "the initiation signal, cPPT, and the termination signal, CTS, ... [were inserted] upstream and downstream [of] the coding sequence of the transgene" as alleged in the Office Action. In other words, a factual basis for the asserted expectation of success is lacking.

In summary, Applicant's claims recite two distinct elements, "a DNA triplex" sequence and "a defined nucleotide sequence" of interest. The claims also recite the interdependence of these two elements, namely, "the DNA triplex transfers the defined nucleotide sequence into the nucleus of a cell." These two elements and their functional relationship are not disclosed or suggested in the cited art.

**Claim Rejections - 35 USC § 112**

Claims 62-65 and 74-77 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, which applicant regards as the invention. Independent claims 62 and 74 both recited the limitation "comprising the vector in a protein envelope." According to the Office, this recitation is confusing because it can be read in two ways: The vector is inside a protein envelope of the non-infectious particle, or (2) the vector is the transgenic protein expressed from the vector in a protein envelope of the particle. Office Action at 2-3. This ground for rejection is respectfully transversed and reconsideration is requested for the following reasons.

New claims 78-85 are consistent with the Examiner's first interpretation of cancelled claims 62-65 and 74-77. "[T]he vector ...[is] inside a protein envelope of the non-infectious particle. Thus, the § 112 rejection may be withdrawn.

Please grant any additional extensions of time required to enter the attached reply and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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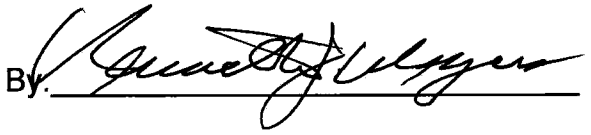
By: 

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